24 143. (Amended) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chain frameworks, which humanized immunoglobulin specifically binds to an antigen, wherein the sequence of the acceptor immunoglobulin heavy chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin heavy chain variable region framework, and the humanized immunoglobulin heavy chain variable region framework comprises at least 70 amino acids identical to those in the acceptor immunoglobulin heavy chain variable region framework, wherein percentage sequence identity is determined by aligning amino acids in said frameworks by Kabat numbering and wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin heavy chain framework outside the Kabat CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, and each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with the CDRs.

[(III)]

REMARKS

Applicants acknowledge with appreciation the courtesies granted by Examiner Reeves during the recent telephone interview.

The cover page of the specification has been amended to reflect the inventorship as corrected in the concurrently filed Petition to Correct Inventorship under 37 CFR 1.48(b). Harold E. Selick, a named inventor at the filing of the subject application, was previously deleted as inventor as a result of cancellation of claims by amendment in the application. The current correction of inventorship results from further cancellation of claims in the application as filed and the addition of new claims, which resulted in Man Sung Co no longer being inventor and Harold E. Selick being properly named as an inventor again. The correct inventors of the presently claimed invention are Cary L. Queen and Harold E. Selick.

Claims 111-126 and 131-144 are pending. Claims 111 and 143 have been amended as suggested by the Examiner with entry of this amendment. Claim amendments are for purposes

of improved clarity or consistency of claim language unless otherwise noted. No claim amendment should be construed as an acquiescence in any ground of rejection. The following refers to paragraph numbers of the Office Action and addresses the issues specifically raised by the Examiner.

Paragraph 5. Oath/Declaration

A new Oath/Declaration signed by the inventors is submitted herein.

Paragraph 8. Claim Rejection Under 35 U.S.C. 112

The Examiner had maintained the rejection of claims 111-112, 115, 116, 139-142 under 35 U.S.C. 112, first paragraph for the alleged lack of enablement for humanization that results in a selected variable region framework which is at least 65% or 70% identical to the donor immunoglobulin variable region framework.

Paragraph 8a

The Examiner expressed the view that the subject specification, the declarations and Exhibits submitted by Applicants with the previous response, only demonstrate alignment between the particular mouse/human framework regions. The Examiner invites evidence that framework regions of other mouse or rodent immunoglobulins will align with human framework regions without gaps.

In response, Applicants submit a further declaration of Dr. Cary Queen under 37 C.F.R. 1.132. Dr. Queen explains in this additional declaration that the same Kabat numbering system is applicable to Ig sequences from both human *and* rodent species (e.g., mouse, rat, and rabbit) as well as the other species listed in the Kabat et al. compendium. Dr. Queen also prepared a composite listing from Kabat et al. that contains both representative human Ig sequences (from subgroup I) and representative mouse sequences (from subgroup IIA), which is attached to his declaration as Exhibit A.

As can be readily seen from Exhibit A, Kabat uses exactly the same numbering system for mouse as for human Ig sequences. As an example, Dr. Queen notes that the four heavy chain framework segments of both human and mouse sequences constitute the same amino acid numbers, and that the intervening CDRs also have the same numbering for human and

mouse sequences. Dr. Queen confirms that the Kabat numbering system provides a unique method of aligning a human Ig heavy chain framework sequence with a mouse Ig heavy chain framework sequence.

Furthermore, Dr. Queen notes in his declaration that not only are there no gaps in the frameworks of the human and mouse sequences when compared within species, there are also no gaps when the human framework sequences are aligned with the mouse framework sequences. It is evident from Exhibit A and Dr. Queen's explanation that the Kabat numbering system provides a unique way of aligning human and mouse framework sequences without gaps, and that the issue of gap weight does not arise for immunoglobulin framework sequences.

In light of the foregoing, it is evident that the framework sequence of a non-human immunoglobulin will properly align with the framework sequences of human immunoglobulins. Therefore, one of skill in the art would be able to use the Kabat numbering system and easily align a donor framework and human acceptor framework sequences to practice the presently claimed methods. Withdrawal of the rejection under 35 U.S.C. 112, first paragraph, on this ground is respectfully requested.

Paragraph 8b

In maintaining the above noted rejection, the Office Action also alleges that the subject specification fails to provide adequate support for the recitation of "identity" in the rejected claims 111-112, 115-116, 139-142. Applicants respectfully traverse.

It is clear throughout the specification that when the acceptor framework sequence is to be selected based on its sequence homology with the donor framework sequence, the two sequences must be at least 65% identical, rather than a mere sequence "homology" as alleged by the Office Action.

Figure 15 of the subject specification provides an example illustrating what "sequence homology" actually encompasses in the subject application. This figure corresponds to Figure 1 in both U.S.S.N. 07/290,975, filed on December 28, 1988, and U.S.S.N. 07/310,252, filed on February 13, 1989, the priority applications of the subject invention. In this figure, the mouse donor anti-Tac heavy chain sequence is aligned with the human acceptor Eu heavy chain sequence. This is precisely the alignment one would need to make to determine the percentage of homology between these sequences. The figure legend (on page 10 of the subject

application) states that: "Identical amino acids in the two sequences are connected by lines." Significantly, there is nothing in the figure to indicate when aligned amino acids represent a conservative change, even though there are certainly conservative pairs in the figure, i.e., leucine - isoleucine at position 70 and serine - threonine at position 76. This would clearly indicate that only identical amino acids are to be counted when determining percentage of homology, i.e., that percentage of homology means percentage of identity.

In addition, Queen et al. (Proc. Natl. Acad. Sci. USA 86: 10029-10033, 1989), which was incorporated by reference in the specification (e.g., at page 188, line 27-29), specifies selecting a more homologous human variable region framework to serve as the acceptor, just as does the subject patent application, and then determines sequence homology by percentage of identity. In this reference, the authors stated:

> The heavy chain V region of the Eu antibody (of human heavy chain subgroup I; ref. 38) was 57% identical to the anti-Tac heavy chain V region (Fig. 2B); [page 10031, right column, second paragraph, emphasis added]

It should be noted that the 57% in the quoted passage refers to percent identity between the entire V regions including the CDRs. The percent identity between only the framework regions is 67%, as may be determined directly from Figure 15, thus meeting the criterion in the subject specification and, e.g., claim 111.

Moreover, other skilled persons have clearly interpreted the subject patent application this way. For example, Gorman et al. (Proc. Natl. Acad. Sci. USA 88: 4181 - 4185, 1991), who followed the teachings of the subject patent application to make a humanized antibody, stated:

> The V_H region of KOL was chosen because of all known human heavy chain V regions its overall amino acid sequence is very homologous to the Campath-9 V_H region (Fig 1A) containing 72% identical residues (excluding gaps introduced for alignment purposes). [page 4182, right column, last paragraph, emphasis added]

For the Examiner's reference, copies of the above cited two articles are attached. It should be noted that the gaps referred to in the above quoted excerpt of Gorman et al. are all within the CDRs of V_H; the framework regions themselves are unambiguously aligned without

gaps, as seen in Figure 1 of Gorman et al.

Finally, unless given specific instructions to count conservative pairs as matches, and instructions as to what amino acid changes count as conservative, none of which was provided in the present patent application, the skilled person would have no choice but to interpret 65% homology to mean that when the sequences are aligned, 65% of the corresponding amino acids are *identical*.

In light of the above explanations, it is clear that 65% sequence "homology" as used in the subject application refers to amino acid sequence identity. Therefore, Applicants respectfully request the rejection under 35 U.S.C. 112, first paragraph, on this ground be withdrawn as well.

Paragraph 11-15. Double Patenting

Terminal disclaimers have been provided.

Paragraph 17. New grounds of Rejection Under 35 U.S.C. 112, first paragraph

Claims 111-113, 115-116, 139-144 are rejected under 35 U.S.C. 112, first paragraph for the alleged lack of support of the recital of "sequence identity." The Examiner expressed the opinion that the subject specification has support for only "sequence homology," and that "sequence identity" is a different concept from "sequence homology." Applicants respectfully traverse.

As the above discussion in addressing issues raised in Paragraph 8b of the Office Action makes clear, the sequence "homology" feature of the subject invention, in the context of comparing the amino acid sequences of the acceptor and donor frameworks, does not encompass conservative substitutions. Rather, it contemplates only identical amino acid residues in the two sequences. As such, the "sequence identity" element as recited in the rejected claims has adequate support in the subject specification. Accordingly, withdrawal of the rejection is respectfully requested.

Paragraph 18. Rejection under 35 U.S.C. 112, second paragraph

Claim 111 was rejected for the alleged indefiniteness in the recital of "predetermined" (paragraph 18a). To expedite prosecution of the instant application, claim 111 has been

amended to replace "binds to a predetermined antigen" with "binds to an antigen." Therefore, the alleged indefiniteness is eliminated. Also, the same claim language as amended is present in U.S. patents issued from the parent application, i.e. U.S. patent 5,585,089. Accordingly, withdrawal of the rejection is respectfully requested.

Finally, Claim 143 has been amended to correct the error as noted in the Office Action (paragraph 18b).

As requested by the Examiner in the telephone interview, a substitute specification has also been provided. The Examiner is advised that the substitute specification has corrected a typographical error in the subject specification as filed. Specifically, at page 43, line 16, the specification as filed incorporated by reference U.S.S.N.'s 07/186,862 and 07/223,037. However, the number 07/186,862 was incorrect; the correct number is 07/181,862. This inadvertent mistake is evident from the fact that the correct U.S.S.N. 07/181,862 was incorporated by reference in U.S.S.N. 07/223,037, which was itself incorporated by the subject specification. For the Examiner's reference, the relevant page from U.S.S.N. 07/223,037 showing incorporation of the correct U.S.S.N. 07/181,862 is attached.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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